



VIRGINIA PROSTATE CENTER **Newsletter**

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Recall of Prostate Cancer Medicine a Disappointment

By Paul F. Schellhammer, M.D.

A very disturbing recall of a prostate cancer medicine occurred during the second week in February. PC-SPES (PC=Prostate Cancer and SPES=the Latin word for hope) was determined to be contaminated by two substances - Coumadin, a commonly used medicine to thin the blood, and Xanax, a commonly used tranquilizer. The amount of contamination, the source, whether intentional or accidental, was not stated. However, the production of PC-SPES was halted and patients who were taking it as treatment were advised to discontinue.

This presents a two-pronged disappointment; the concern that medication is associated with harmful and unknown side effects and the concern that a successful treatment must be interrupted for some time period.

PC-SPES has gained attention because of the benefits it offers some prostate cancer patients. This success and its recall prompted the following discussion:

Because of its occasional very dramatic effect in the treatment of androgen independent prostate cancer, PC-SPES, a mixture of 8 Chinese herbs, has awakened physician interest in and directed their attention to the ground swell of patient and public enthusiasm for herbal remedies, dietary modifications, vitamins, min-

erals and supplements. What not so many years ago was considered "alternative medicine," perhaps a euphemism for quackery, has moved steadily into the realm of acceptance as indicated by the current "complementary or integrated medicine," and now is beginning to reach the mainstream of traditional care.

Only a fraction of the approximately 250,000 species of higher plants have been systematically investigated for the presence of bioactive compounds. There is a wealth of therapeutic potential locked in nature's flora - a fact that has not escaped the public and cancer patients in particular. An estimated 85% of cancer patients use over-the-counter vitamins, supplements, and herbals with the expectation that they will, at best, provide cure or prolongation of life and, at a minimum, improve quality of life. The Prostate Cancer Prevention Trial (PCPT) showed that 60% of the trial participants recorded dietary supplement use. Participation by patients in their healing process and control of their health and destiny are oft-cited objectives of self-medication.

However the uncertainties and dangers are legion. No information is available concerning dose response or interactions with conventional agents. Only well conducted clinical trials can provide evidence of efficacy as

monotherapy or in combination with other therapies. This is a time- and cost-intensive effort.

There is also very little information on the constancy of dose, compound stability, percent of active ingredients, and safety profile. Presumably, a set of regulations awaiting confirmation will help protect the public by providing assurance that at least "what they see (read) is what they get (buy)." Its implementation can come none too soon.

In 1938, the Food, Drug, and Cosmetic Act (FDCA) was passed to mandate that pharmaceutical agents to be sold to the public had to be safe. The 1962, Kefauver-Harris amendment to the FDCA mandated that pharmaceutical agents to be sold to the public had to be effective. In 1994, however, the Dietary Supplemental Health and Education Act permitted over-the-counter sale of herbal products and vitamins with minimal regulatory oversight.

However, provocative information has recently appeared in peer-reviewed manuscripts. Consider lycopene, the pigment that gives tomatoes their red color. North Americans get between 85% and 90% of their dietary lycopene from tomatoes. It can also be found in the foods like watermelon and pink grapefruit. Lycopene is an antioxidant and as such might prevent the DNA damage

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Identifying the Selfish Transcriptome

By Jose Ignacio Diaz, M.D., Ph.D.

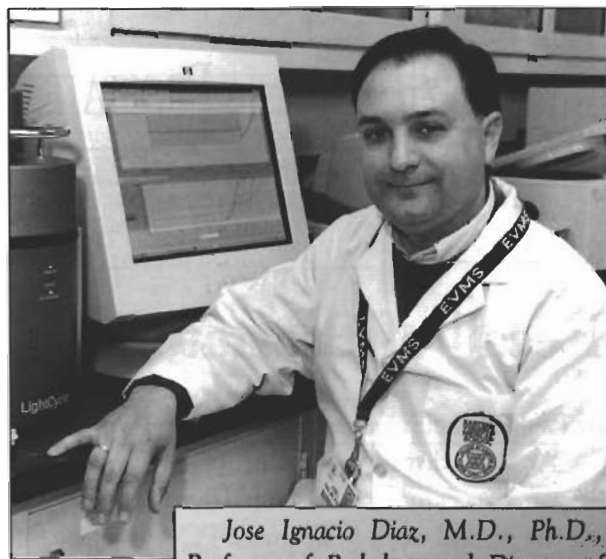
Carcinogenesis, the process by which cancer develops, is a multi step process where a progressive accumulation of genetic alterations leads to dysfunction of the genes controlling cell growth, survival and differentiation. These events can be summarized in four steps: neoplastic transformation, clonal expansion, local invasion and metastasis.

Following neoplastic transformation, an ancestral cell emerges, which is capable of uncontrolled overgrowth. In contrast with reparative overgrowth, neoplastic overgrowth has no beneficial purpose for the host and is persistent. The clonal expansion of this ancestral cell ensures a tribal progeny of cells with the same ability to overgrow. But cancer is more than a disorder of cellular overgrowth. The more aggressive or spreading forms of neoplasia, known as cancers, are also capable of invading and destroying adjacent normal tissues as well as traveling and colonizing distant organs, a process known as metastasis, which accounts for the high mortality associated with cancer.

Carcinogenesis is a time-dependent, evolutionary process. With time, tumors become more aggressive, a phenomenon known as tumor progression that implies the sequential appearance of subpopulations of tumor cells with newly acquired growth, invasive and metastatic attributes. As in a decathlon, subpopulations of malignant cells surmount numerous hurdles before achieving successful metastases, which include: detachment from each other, breaking through their own basement membranes, moving in the interstitial matrix, crossing the vascular basement membranes, surviving the voyage of lymph or blood circulation, crossing back in reverse order from the capillary lumens, moving in their new extracellular matrix and surviving in their new environment, re-establishing

their own blood supply and escaping the host immune surveillance. Only certain subclones of tumor cells will ever express the right combination of genes allowing them to surmount these hurdles. Only those tumor cells equipped with the appropriate machinery for this difficult voyage will survive.

Tumoral and non-tumoral living cells perform their biological functions through activation or repression of specific genetic programs. DNA, the master molecule of life, is a lineal array of genes containing all the information necessary to fabricate the proteins, which are the specialized biological workers that execute all the functions of the living cell. Most of these functions require the collaboration of a team of proteins encoded in a set of genes or genetic program. All the genes present in the DNA of an organism constitute its genome, while the combination of the specific genes expressed by the cell is called the transcriptome. The Human Genome is made of no more than 30,000 to 40,000 genes. Surprisingly, this number is not much higher than the number of genes in the little mouse. The living cells can probably elaborate several millions or even billions of different transcriptomes by expressing various combinations of these genes, which means that small differences in gene number may translate in great differences at the transcriptome level. The transcriptome of individual cells is continuously remodeled through a complex network of signals that allow the cells to respond to the needs of the environment. Cells receive external signals that activate or repress their genes, dictating when they should grow, when they should die or when they should differentiate into specific cell types.



Jose Ignacio Diaz, M.D., Ph.D., Professor of Pathology and Director of Molecular Pathology, Department of Pathology and Anatomy, joined the EVMS faculty in January 2002. Dr. Diaz received the M.D. degree in 1982 and Ph.D. degree in 2000 from Autonoma University of Madrid, School of Medicine. He received his residency training in pathology at EVMS and the Cleveland Clinic Foundation. Dr. Diaz served as Director of Molecular Pathology at Florida Hospital, and was an Associate Professor at the H. Lee Moffitt Cancer Center and Research Institute in the Division of Urology, Departments of Pathology and Surgery, before arriving at EVMS.

Malignant cells establish their supremacy over the host by expressing a "selfish transcriptome," which cancels the social contract with the host. In many ways, the biological behavior of malignant cells is the result of "cell selfishness" genetic reinforcement. In the social context of a complex multicellular organism, the general features associated with malignancy, such as undifferentiation, prolonged survival and overgrowth are features of selfishness. Cancer cells compromise the life of the host as selfish individuals compromise the social order, sharing a similar destiny of self destruction.

The characterization of the specific

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Recall

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that might occur in an oxidatively stressed prostate. These findings call for scientific trials of lycopene and tomato products.

In conclusion, it is clear that nature's remedies will play a future role, and this role must be supported by basic and translational research and clinical trial evidence. In the interim, physicians must not turn their backs on this burgeoning arena of health-care. They are well advised to become familiar and conversant with the current evidence so as to maintain their patients' confidence, provide them direction, safeguard them from harm, and, hopefully, by clinical observations and careful scientific research, advance the field to therapeutic benefit. ■

Selfish Transcriptome

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transcriptomes associated with cancer could highlight many relevant molecular targets and provide the rationale to develop more specific cancer treatments in the future. However, this task is not an easy one. While tumors are clonal in origin, at the time of clinical diagnosis they are composed of a heterogeneous mixture of tribal subpopulations, each of them with significant differences, which makes cancer an extremely complex disease. In the past we have not been able to evaluate tumor heterogeneity appropriately because we were lacking satisfactory methodological approaches. The implementation in recent years of high-throughput gene expression techniques, such as oligonucleotide microarrays and proteomics and our ability to rescue selected tumor cell populations from tissues with laser capture microdissection is beginning to solve this problem. These techniques very often generate an excessive amount of data requiring further val-

Paul Sawyer establishes research fund in support of prostate cancer

A generous donation by Mr. Paul Sawyer will ensure and support continued research in the field of prostate cancer, under the auspices of the Virginia Prostate Center, a program sponsored and supported by Eastern Virginia Medical School and the Sentara Cancer Institute. The grant will provide support for physicians and scientists currently associated with the VPC and provide support for future physicians joining the VPC program.

Mr. Sawyer met Paul Schellhammer in 1973 when Mr. Sawyer was seeking consultation for recently diagnosed prostate cancer, and Dr. Schellhammer was a fellow in training at Memorial Sloan-Kettering

Cancer Center. After successful therapy, Mr. Sawyer returned home to Virginia Beach. Unbeknownst to Mr. Sawyer, Dr. Schellhammer joined the Devine-Tidewater-Poutasse practice in Norfolk. While visiting his wife at Norfolk General Hospital in the late 1970's, he heard Dr. Schellhammer's name called over the hospital page system. They re-established contact and Paul Sawyer has been a strong supporter of the clinical and basic research effort of the Virginia Prostate Center since.

In making his most recent contribution, Mr. Sawyer expressed the interest that provisions be made for continuity of patient care and the prostate cancer research program currently in place. ■

idation and characterization of the identified candidate genes and proteins. The use of tissue microarrays containing a large number of well characterized tumors could be an invaluable resource to validate these results.

In summary, with the beginning of this new century we have developed a much better armamentarium for understanding and solving the problem of cancer. The recent completion of the Human Genome Project is the beginning of a new era for biomedical sciences, which will be characterized by accurate predictability. It is conceivable that during the next few years the systematic approach of studying gene expression profiles in multiple tumors, patients and tumor cell subpopulations will elucidate which are the genes and proteins involved in all the steps of malignant transformation and more importantly, which are the most critical ones. The newly identified molecular targets could provide more accurate diagnosis, better prognostic predictions and more specific and effective cancer treatments. This

could be particularly helpful in prostate cancer. While a minority of prostate cancers are lethal, many others are slow growers, not compromising the life expectation of the patient. Our ability to make this prediction at the present time is unsatisfactory. Identifying the genes and proteins responsible for prostate cancer's aggressive behavior will allow us to make this prediction reliably. The Human Genome Project was recently completed but the monumental challenge of identifying the "selfish transcriptome" have just begun. The members of the VPC are part of a community of dedicated cancer researchers enthusiastically committed to this monumental endeavor. As a genitourinary and molecular pathologist, I will have the honor to help on this collective effort by ensuring excellent tissue procurement, selecting the tumor cell populations to be microdissected and submitted for proteomics and helping to design new validation strategies such as tissue microarrays or any other complementary gene expression molecular techniques. ■